REMARKS

Claims 1-5, 8, 12 and 13 are pending in the present application. Claims 6, 7, 9-11, 14-21, 23-28, 33-35 and 37-45 have been cancelled without prejudice. Claims 22, 29-32 and 36 have been withdrawn from consideration as drawn to a non-elected invention.

Claim 46 has been added and is directed to a method of treating arthritis by administering the recited agents to the subject as the only essential elements. The language "consisting essentially of" excludes any other material steps or additions and the following Markush language excludes any other material agents, such as, e.g., IL-8. The transitional phase "consisting essentially of" limits the scope of the claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristics" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original). Support for this claim is found throughout the specification and including, in the working examples. (See specification at page 34 through page 45).

Reconsideration of the pending claims is respectfully requested in view of the following remarks.

Applicants, through the undersigned, thank Examiner Woodward and Nickol for the courtesy extended on behalf of the applicants in respect to the extensive interviews conducted May 19 and May 24, 2010 in this case.

Claims 1-5, 8, 12 and 13 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Develaraja, et al. (U.S. Publication 2007/0059280) (hereinafter "Develaraja, et al.") and as allegedly evidenced by the cited art of record.

As claimed, the present invention is directed to treating arthritis with an antibody to G-CSF, an antibody to G-CSFR, or a soluble G-CSFR and a G-CSF binding fragment,

wherein the recited agents inhibit the activity or level of expression of G-CSF or G-CSFR. The present inventors are the first to demonstrate the independent effect of the inhibition of G-CSF or G-CSFR in the treatment of arthritis as supported by actual *in vivo* data.

Devalaraja, et al. is not an enabling prior art reference. The statements or proposals regarding the treatment of arthritis in the Devalaraja, et al. disclosure are unsupported and, in fact, contradicted in the same disclosure. In the context of the relevant prior art, the reference fails to establish any clear teaching respecting G-CSF and is therefore not enabling.

In the first instance, the record of the Devalaraja, et al. application reflects a rejection under 35 U.S.C. §112, first paragraph, for lack of enablement in respect to the administration of an antibody to M-CSF for the treatment of rheumatoid arthritis. This rejection was only overcome by the submission of actual *in vivo* animal data. (See Exhibit A).

While M-CSF and G-CSF are distinct, the point is that the Devalaraja, et al. reference is less supportive of the disclosure of G-CSF in the context of treating arthritis than M-CSF which was rejected on the same grounds for lack of enablement. Moreover, the data reflected in the Devalaraja, et al. reference with respect to G-CSF is actually contradictory, particularly as it relates to IL-8. Furthermore, no actual *in vivo* data is ever presented. At best, it is at least wholly inconsistent to conclude that Devalaraja, et al. is enabling for G-CSF in the treatment of arthritis in the absence of some *in vivo* data which does not appear in the reference. In this regard, consider the uncertainty and complexity reflected by the relevant prior art extant at the time of the reference disclosure. (See Exhibit B).

Further, the therapeutic methods described by Devalaraja, et al. are based on an observation of the **synergistic** effect of **exogenously added** G-CSF on chemokine mediated inflammation, i.e., neutrophil recruitment. On proper analysis, Devalaraja, et al. only

discloses the potentiating effect of G-CSF on IL-8 mediated chemotaxis. Consider further, in this regard, that Devalaraja, et al. disclose experimental data in the same disclosure which actually contradicts the potentiating effect of G-CSF on IL-8 mediated chemotaxis.

In this regard, the Examiner must also consider that the effects of G-CSF itself were not evaluated by Devalaraja, et al. and the proposed therapeutic effect **depends entirely on positive synergy with IL-8**. In addition, Figures 8 and 12 of Devalaraja, et al. show that pre-treatment with G-CSF actually **decreased the effects of IL-8 on neutrophils**. These findings are interpreted by Devalaraja et al. as evidence of 'interactions' between the two cytokines. However, interactions could have positive, synergistic effects, or produce a countervailing, negative effect. In terms of G-CSF and IL-8, the data shown by Devalaraja, et al. contradicts a claim of positive synergy between the cytokines. On the basis of Figures 8 and 12, inhibitors of G-CSF would be predicted to enhance the pro-inflammatory effects of IL-8, because G-CSF decreased the responses to IL-8. This is the **opposite** of the desired effect in treating an inflammatory disease, i.e., an inhibitor of G-CSF would reduce the purported antagonistic effect of G-CSF on IL-8, allowing it to act in an unrestrained manner**.** A skilled artisan would certainly be confused by the data and unable to draw any meaningful conclusion. (See, Exhibit B, the Declaration of Dr. Ian Wicks at paragraph 5).

The Examiner asserts that the Devalaraja, et al. reference provides detailed methodologies and evidence of predictability. It is unclear how the prior art reference can provide evidence of predictability when the results disclosed are conflicting at the point of issue.

Applicants have also considered the criteria set out by the Court in *In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), in respect to the teachings of the cited reference to Devalaraja, et al.

1. Nature of the Invention: The nature of the invention is very complex and unpredictable. Such is the nature of most biological technologies. (See also, Exhibit B, at paragraphs 7-9).

2. State of the Prior Art: The state of the prior art was wholly unpredictable and unresolved. The literature at the time of the Devalaraja, et al. disclosure taught that G-CSF exhibits immuno regulatory effect of dendritic cells and T-cells that would favor immunosuppression in CIA. (See, for example, paragraphs 10, 12 and 13 of Exhibit B).

3. Relative Skill of those Skilled in the Art: The relative skill is generally high in the biological arts.

4. Level of Predictability: Consider, for example, Exhibit B, paragraphs 10, 12 and 13, which demonstrate the unpredictability of the prior art. Moreover, as shown above, the cited reference to Devalaraja, et al. is actually contradictory in and of itself. See Examples 8 and 12 of the cited reference specifically.

5. Evidence of Working Examples and 6. Direction or Guidance Provided by the Inventor: The reference to Devalaraja, et al. evidences absolutely no *in vivo* data and the amount of direction or guidance provided by Devalaraja, et al. is not only completely lacking but the supporting data is **contradictory** in the same reference. See, Examples 8 and 12 of the Devalaraja, et al. reference.

7. Quantity of Experimentation: Recognizing that *in vivo* experimentation is necessary to demonstrate the proposed activity of the reference and is required to reconcile the inconsistencies of the teachings of the reference, those skilled in the art would readily conclude that the experimentation, considering all the *Wands* factors, is in fact, **undue**. See, Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 89 USPQ 2d 1370 (Fed. Cir. 2008).

Applicants observe that the Examiner's comments on "undue experimentation" relate to the non-disclosure of an *in vivo* model in the cited prior art reference. The Examiner has not, however, addressed the conflicting results disclosed in Devalaraja, et al. It is "undue experimentation" to determine whether the intended effect or opposite effect is actually correct.

Notably, in response to all of the evidence presented by the applicants, the Examiner has cited a prior art reference that relates to GM- CSF. The Examiner states that Devalaraja, et al. and *Cook, et al.*, Arthritis Res. 11, June 2001:3:293-298, provide detailed methodologies and evidence of predictability of the claimed invention because of the predictive nature of the art relating to growth factors.

In the first instance, however, it is unclear how Devalaraja, et al. can be found to be predictive of anything - will it enhance pro-inflammatory effects or not? To make such a determination in the present context, requires undue experimentation.

With respect to Cook et al, while the colony stimulating factors have similar names, these are unique and quite different cytokines (http://www.copewithcytokines). In keeping with different genetic loci and protein structural differences, these cytokines have different functional activities. G-CSF has a narrow range of activities relating to the production, function and survival of neutrophils. G-CSF is produced by a variety of cells including macrophages, endothelial cells and fibroblasts. The G-CSF receptor (G-CSFR) is a unique, single transmembrane structure, that is primarily expressed by neutrophils and their precursors.

In contrast, GM-CSF has a much broader range of activities, including the production and function of neutrophils, macrophages, erythroid and megakaryocyte progenitors,

eosinophils and dendritic cells. GM-CSF is produced by monocytes, endothelial cells and fibroblasts as well as activated T cells. GM-CSF signals through a dimeric receptor, composed of a unique, low affinity ligand binding alpha chain and a signal transducing common beta chain that is shared with the cytokines IL-3 and IL-5. The GM-CSF receptor is primarily expressed on myeloid cells and endothelial cells. These differences do not translate from one growth factor to the other. In view of these differences, and the literature on G-CSF cited by the applicants, the work of Cook et al on GM-CSF could not be simply translated to G-CSF.

While the colony stimulating factors have some level of overlapping action, it is also the case that each of the factors has its own unique properties. A disease such as rheumatoid arthritis is very complex with a multiplicity of factors and cytokines, not just the colony stimulating factors, being implicated. In this context, it is in fact surprising that modulating any one factor can have a significant impact on disease, and the art is in fact highly unpredictable. In the context of the limited data provided by Devalaraja, et al. taking into account the seemingly contrary data provided in Figures 8 and 12, those skilled in the art would have been highly skeptical of the proposed method.

> In the period following the discovery of the CSF's other regulators of hematopoietic populations were discovered, resulting in a confusing picture of the further potential redundancies or interactions in the control system. For example, granulocyte colony formation *in vitro* can be simulated by G-CSF, GM-CSR, M-CSR, IL-3, SCFR, IL-6 and weakly by IL-11 (REF. 28). In particular, the CSF's seemed to have many biological actions that were potentially overlapping or redundant, and it required gene knockout studies in mice in the mid-1990s to establish that each CSF did, in fact, have actions that were exclusive to that CSR.

Metcalf, *The Colony-Stimulating Factors and Cancer;* Nature Reviews/Cancer, Volume 10, June 2010 at page 427.

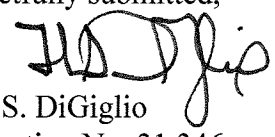
Each of the colony-stimulating factors is different and what may be relevant for

one is not a good predictor of what may happen with another one. With this knowledge of the differences between the CSFs and considering the multi-factorial nature of rheumatoid arthritis that includes numerous factors beyond the CSFs, it is only in the light of data from a validated animal model of rheumatoid arthritis that those skilled in the art would reconcile that targeting a particular single factor such as G-CSF is useful in the therapy of rheumatoid arthritis.

Accordingly, Devalaraja, et al. is not an enabling reference. The rejection under 35 U.S.C. §102(e) is obviated and withdrawal thereof is respectfully requested.

Thus, in view of the foregoing amendments and remarks, it is firmly believed that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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